IN THE SPECIFICATION

Kindly replace paragraphs [0002], [0004], [0006], [0007], [0011], [0015]- [0030] and [0032]-[0035] of the specification of Applicants' U.S. Patent Application Publication No. 2002/0128704 with the paragraphs shown below.

[0002] The present invention relates to implantable devices, such as stents, used for implantation in tissue for cardiovascular intervention and other purposes, and the delivery of drugs placed on or in the stent. In particular, the present invention relates to a stent prepared to deliver drugs when heated by electromagnetic fields, and a method and system for causing drug-coated or drug-loaded stents to deliver their drugs into the blood stream of a cardiovascular vessel or into surrounding tissue.

[0004] Stents can be coated or loaded with different drug formulations, including materials such as biologically active micro-spheres used for controlled release of biologically active agents inhibiting restenosis of the stent. These drugs can be included in encapsulations, such as polyethylene glycol substances, that are formulated to dissolve within a period of time to release the biologically active micro spheres into the vessel wall of the organ or the vessel in which the stent is located.

[0006] An object of the present invention is to provide a mechanism for controlling the delivery or activity of a drug placed on or in a drug-delivery stent, and to provide such control ~~non-invasively~~, in a non-invasive manner, from outside of the patient's body. In German Gebrauchsmuster DE 295 19 982.2 and in European patent application EP 1 036 574 A1, inductive or hysteresis-loss methods for heating up stents non-invasively with electromagnetic fields have been presented. The stated purpose of this heating is to prevent or retard cell growth in the regions adjacent the stent. The heating of the stent is contemplated to be sufficient to render the cells adjacent the stent non-viable.

[0007] During inductive heating as described in, e.g., patent DE 295 19 982.2, the stent heats up from normal body temperature of 37.6° C to higher temperatures, typically above 40° C. The heat energy can then be used in several different ways to control activity of a drug that is coated on or

loaded in a stent. First, the heat within a stent can be used to activate a heat_sensitive drug-releasing material (e.g., a fiber) from which the stent is made. The heat thus makes available a drug that is otherwise captured within the stent material and is wholly or largely not available for activity with adjacent tissue. With a properly-selected drug-releasing material, the opposite effect is also possible, i.e., that heat deactivates the material or prevents or inhibits its release. Second, the heat within the stent is conducted by thermal heat conduction to the outer surface of the stent. If a drug coating is at that surface, the heat can be used to activate a drug that is wholly or largely inactive at normal body temperatures. Alternatively, if the drug is contained in a heat-sensitive release coating that is on the stent surface, the heat energy at the stent surface can cause the drug to be released, so that it can diffused or dissolved into adjacent tissue. Again, with a properly selected drug formulation, heating to cause drug deactivation or inhibition of drug release is also possible. Third, as the heat energy at the stent surface travels by heat conduction into the tissue adjacent the stent, the proteins and other molecules in the tissue will also become heated. Thus, not only is the drug released, but the microenvironment in which the drug and adjacent tissue interact will be heated. This heating may enhance or otherwise affect the drug-tissue reactions in ways that are not present when one or both are at lower temperatures.

[0011] Although stents prepared with variety of drugs that can be delivered in this way are possible, one application is a stent bearing a drug that would help prevent restenosis from occurring. We propose a stent to deliver or activate a restenosis-preventing drug. The drug may be located directly on the surface of the stent or within the stent or inserted in an encapsulation layer on the surface of the stent. In all cases, the stent-carried drug will not be available or be active at body temperature, but it becomes available or active at a certain temperature point above body temperature. (The reverse effect of a drug active at body temperature and selected to become inactive is also possible and may be useful.) The invention also involves a treatment method. In order to make the drug available or active at the stent surface, the stent with the drug has to be heated. The patient will come to the hospital in a defined sequence to be treated for a certain period of time with stent heating to certain temperatures selected based on the drug and/or its encapsulation and/or the drug_tissue interaction at various layers. The drug then will be delivered into or at the patient's blood or vessel wall.

[0015] FIG. 1 shows an embodiment of the present invention. A thin-walled stent 20 ~~of~~ having a generally cylindrical shape is shown inserted within a tissue, where such tissue 10 may be the interior of a blood vessel with opposing walls ~~10~~ enclosing the stent 20. On the exterior of the stent 20 is a layer of drug material 40, which is in direct contact with the tissue 10. (In reality, the stent 20 will normally be woven wires or a grid of some kind; thus, the "exterior" of the stent 20 is not solely the outer surface of the cylindrical form of the stent, but also includes other portions of the stent 20 that contact the tissue 10, whether these are on the outer surface of the cylindrical form or the inner surface or interstitial surfaces in between the two.) In this embodiment, the drug material 40 comprises an active drug dispersed in an encapsulation material that prevents the active drug from having effective contact with the tissue 10 at normal body temperatures. However, at elevated temperatures, the encapsulation material that is part of the drug material 40 breaks down to release the active drug and ~~permit~~ permits molecules of the active drug to interact with molecules of the tissue 10.

[0016] For example, the active drug can be a restenosis-preventing drug. The restenosis preventing drug is inserted into or encapsulated in a biodegradable polymer, such as a polyethylene glycol composition, to form the drug material layer 40. The stent 20 is then heated at a temperature of 39°C and the biodegradable polymer dissolves. This makes the drug available to contact or interact with the tissue 10 surrounding the stent 20. In fact, the drug will in most cases diffuse somewhat into the surrounding tissue, thus making its active effect available not only at the exterior of the stent 20, but also at small distances therefrom. Preferably, the heating is applied non-invasively. This can be ~~done by~~accomplished with a radio frequency generator device that generates an electromagnetic field sufficient to cause inductive (and/or hysteresis loss) heating in the stent. Such devices are described in Gebrauchsmuster DE 295 19 982.2 and in European patent application EP 1 036 574 A1. When the inductive heating treatment is ~~turned~~shut off, the stent 20 will cool down to normal body temperature and the heat-activated process ~~stops~~terminates. This procedure can be repeated several times. (As noted above, the opposite effect is also possible, i.e., that heat deactivates the material or prevents or inhibits release.) As long as the supply of the drug material is not exhausted, more of the encapsulation layer will break down and more of the active drug will be released.

[0017] Another embodiment is shown in FIG. 2. A thin-walled stent 120 ~~of~~ having a generally cylindrical shape is shown inserted within a tissue, where such tissue 110 may be the interior of a blood vessel with opposing walls ~~110~~ enclosing the stent 120. On the exterior of the stent 120 is a layer of drug material 140, which is in direct contact with the tissue 110. (In reality, the stent 120 will normally be woven wires or a grid of some kind; thus, the "exterior" of the stent 120 is not solely the outer surface of the cylindrical form of the stent, but also includes other portions of the stent 120 that contact the tissue 110, whether these are on the outer surface of the cylindrical form or the inner surface or interstitial surfaces in between the two.) In this embodiment, the drug material 140 comprises ~~an active~~ a drug that is formulated ~~so~~ such that it has substantially no effect on the tissue 110 at normal body temperatures. However, at elevated temperatures, the ~~active~~ drug undergoes a change that makes it active. Thus, the previously substantially inert molecules of the ~~active~~ drug begin to interact with molecules of the tissue 110. (As noted above, with a properly selected drug formulation, heating to cause drug deactivation or inhibition of drug release is also possible.) This effect can be achieved by heating that causes changes in the activity level of either the ~~active~~ drug with which the stent is coated or by changes in the activity level of proteins or other molecules in the tissue 110 with respect to the ~~active~~ drug. That is, heating may have an effect on the reaction speed or nature of the interaction of the ~~active~~ drug and the tissue 110 at the drug-adjacent tissue interfaces.

[0018] A further embodiment is shown in FIG. 3. A stent 220 of generally cylindrical shape is shown inserted within tissue, where such tissue 210 may be the interior of a blood vessel with opposing walls ~~210~~ enclosing the stent 220. The walls 240 of the stent 220 are impregnated or loaded with a drug material, which is mainly not in direct contact with the adjacent tissue 210. In this embodiment, the drug-loaded walls 240 contain an active drug that is formulated into the wall material so that it has substantially no effect on the adjacent tissue 210 at normal body temperatures. However, at elevated temperatures, the active drug is released from within the walls 240. Thus, the previously substantially unavailable molecules of the active drug begin to interact with molecules of the adjacent tissue 210. This effect can be achieved by heating that causes changes in the binding of the active drug with which the stent is loaded or by actual dissolution of the walls 240 loaded with the active drug. That is, heating may have an effect on the release of the active drug from the walls 240 or the integrity of the walls 240. In either event, the heating of the

stent causes increased availability of the active drug at the drug-adjacent tissue interfaces.

~~EXAMPLES~~

[0019] The ~~herewith~~present claimed ~~method~~methods for ~~of~~ heating stents to ~~heat~~deliver a drug layer applied to the stent ~~and heat surrounding tissue~~ may help other drug delivery techniques to deliver their drugs in a controllable or selective way. Examples of this are as follows:

~~EXAMPLES ARE~~

[0020] In U.S. Pat. No. 5,980,566, an iridium oxide coating for a stent has a biodegradable carrier of drugs applied thereto for beneficial localized action, as by incorporating into the carrier along the inward-facing surface an anticoagulant drug to reduce attachment of thrombi with blood flow through the lumen of the stent. Heat delivered, ~~through~~ per the claimed methods of the present invention, ~~as claimed here~~ could selectively enhance the drug release or and therefore the drug availability which in turn would ~~to~~ help the process to reduce the attachment of thrombi with blood flow through the lumen of the stent.

[0021] In U.S. Pat. No. 5,980,551 (see also PCT application W098/34669), a stent has biologically active micro spheres that release a biologically active agent into the vessel wall or organ. To inhibit restenosis of the stent, the biologically active micro spheres include encapsulated PGE1 in a water soluble polyethylene glycol mix. The temperature ~~increase~~ elevating process, ~~as described here~~of the present invention, could help to selectively control the period of time required to dissolve and release the PGE1 into the vessel wall or organ.

[0022] In ~~the~~ U.S. Pat. No. 5,980,551, an anti-coagulation drug is incorporated into a biodegradable material to form a liquid-coating material. The temperature elevating process, as described in the present invention, could help to continue this integrated coating, which is less than about 100 microns.

[0023] In ~~the application described in~~ U.S. Pat. No. 5,733,327, the temperature elevating process, described in the present invention, could help selectively control the dissolution mechanism of poly-e-caprolactone, poly-D, L-deca-lactone, poly-dioxane and copolymer.

[0024] In ~~the application described in~~ U.S. Pat. No. 5,700,286, the temperature elevating process, as described in the present invention, could help enhance effectiveness ~~for~~of the lubricious material, which can be polyethylene, oxide, polyethylene glycol, polyethylene acetate, polyvinyl pyrrolidone, polyvinyl alcohol, polyacrylamide, hydrophilic soft segment urethanes, some natural gums, polyanhydrides or other similar hydrophilic polymers, and combinations thereof.

[0025] In ~~the application described in~~ PCT patent WO 00/56376, the temperature elevating method, as described in the present invention, could help to selectively degrade devices formed [[of]]from polyhydroxylkanoates. These are taught as used in conjunction with metal that can be inductively heated.

[0026] In ~~the application described in~~ German patent application DE 197 37 021 A1, the method, as described in the present invention, could help to selectively oxidize the medical implant which is made of magnesia, iron or zinc or other suitable materials.

[0027] In ~~the application described in~~ PCT application WO 96/33757, the temperature treatment of the present invention could help to selectively control the process of dissolving the surface coating with a physiological acceptable polymer, such as polyvinyl alcohol or fibrinin, containing a nitrosol compound dissolved or dispersed therein ~~a nitroso compound~~, such as 2-metyhyl-2-nitrosopropane.

[0028] In ~~the application described in~~ German patent application DE 195 14 104 A1, the method as described in the present invention, could support the selective dissolution of the drug, such as poly-D, L-lactide, thrombine inhibitors and other derivates.

[0030] Heating of stents as contemplated by this invention can be performed with metallic stents having adequate magnetic permeability or field absorbing qualities according to the teachings of

German Gebrauchsmuster DE 295 19 982.2 and European patent application EP 1 036 574 A1. (The disclosures of these are incorporated by reference.) In these, electromagnetic fields are generated at a coil or other sending antenna, ~~and~~ the stent is placed in the field with an orientation and at a distance and location that permit sufficient power to be absorbed at the stent (acting as a receiving antenna), such that heat can be generated in the stent. The amount of heat energy delivered to stent and the duration of heating are important variables for the drug activity selective control contemplated by this invention. The electromagnetic energy may be provided in controlled, brief pulses to permit a more precise control of the energy delivered to the stent and resulting heating effects. The greater the control of heating, the greater the control of the resulting drug release, or drug activation or drug-adjacent tissue reaction enhancement.

[0032] It is appreciated that besides stents, any other type of suitable implantable devices can be used within the scope and spirit of the present invention to controllably elute a drug ~~off-of~~from an implantable device. Also, the implantable devices may be used just for the purpose of eluting drugs into the body. One of such implantable devices may be a metallic hip, joint which is coated with a drug for better biocompatibility. The drug may be eluted by an increase in temperature. Also, a device may be made as a ball shaped type or as many small pills which are implanted just to be heated inductively to elute the drug. Thus, the invention is applicable to any implantable object (whether or not it has a prosthetic or other function) that has the ability to be heated in the manner described herein so as to cause drug release and that can be placed in a position at which or from which drug delivery is desired.

[0033] It is also appreciated that the devices can be temporarily implanted or permanently implanted. These ~~device~~devices may be used to help chemotherapy or any other therapy.

[0034] One exemplary application can be to implant a metallic coil or pellet in the patient's prostate and use the ~~above-described~~present invention to control the elution of a drug to treat a prostate disease. Other exemplary applications may be to control the elution of insulin ~~off-of~~from an implantable device in a diabetic patient, or to control the elution of a drug ~~off-of~~from an ophthalmic device in the eye to treat vision related diseases.

[0035] Accordingly, the present invention provides an implantable device having at least one coated drug material capable of being heated inductively and delivering the drug material upon heating to a body ~~when heated~~. The frequency of the inductive heat is preferably below 1 MHz. Under 1 MHz, the body tissue is generally opaque for radio frequency inductive heating, above that frequency the body tissue absorbs the energy and is heated itself.